

REMARKS

Claims 26, 34 and 41 have been canceled. New claims 45-47 have been submitted. The newly submitted claims specify crystals used in the claimed methods belong to particular spacegroups. This limitation was previously present in Claims 28, 36 and 42 but is now removed from those claims and presented in dependent claim form.

Claims 24, 25, 33 and 39 have been amended. The term “computational means” has been changed to read “computer program means”. Support for the use of computer programs can be found in the specification, for example, on page 143, lines 3-21. This section also references PCT Publication No. WO 95/35367, by Wilson et al., which was incorporated by reference and which teaches specific computer programs for performing the designated functions.

Claims 28, 36 and 42 have been amended so that the proteins used to generate crystals are at least about 80% homologous to the stated SEQ ID NO's. Support for such proteins can be found in the specification, for example, on page 136, lines 14-22, through page 137, lines 1-3. These claims have also been amended to remove reference to a particular space group.

Claim 32 has been amended so the three-dimensional model constructed in step (a) is utilized in step (b) to perform structure-based design.

Claims 37 and 43 have been amended to correct the lack of antecedent basis noted by the Examiner. Specifically, these claims now refer to the Fc ϵ R α I protein and IgE antibody of Claims 32 and 39 respectively.

Claim 39 has been amended to correct the antecedent basis problem noted by the Examiner. Specifically, the claim has been amended so that the three-dimensional model constructed in step (a) is used in step (b) to screen structures obtained from a database.

Claim 40 has been amended to correct the lack of antecedent basis noted by the Examiner. Specifically, Claim 40 now refers to the “structure identification” step of Claim 39.

In view of the above, Applicants submit no new matter has been entered into the Application.

Rejections under 35 U.S.C. §112, first paragraph – written description

The Examiner has rejected Claims 24-26 and 28-44 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner has stated Claims 24-26 and 28-44 are newly introduced claims which have no basis in the specification. Therefore, this is a new matter rejection.

The Examiner has stated Claims 24, 25, 33 and 39 recite “computational means” but the specification fails to disclose this generic concept or what was intended to be embraced by this concept. While Applicants believe the term “computational means” was adequate, for the sake of expediting prosecution, Applicants have amended Claims 24, 25 33 and 39 to specify “computer program means”. This limitation is clearly supported in the specification, for example, page 143, lines18-21, which state there are a number of computer programs, known to those of skill in the art, for designing and screening inhibitory compounds. Moreover, the cited section incorporates by reference PCT Publication No. WO 95/35367, which lists specific computer programs for performing the above-mentioned functions. The Examiner is directed to PCT Publication No. WO 95/35367, specifically page 22, lines3-40, through page 24, lines 1-13, which list 10 specific computer programs for analyzing three-dimensional models. In view of the above, Applicants believe there is adequate written description to support “computer program means.”

The Examiner has rejected Claims 26, 34 and 41, stating these claims recite the steps of obtaining or synthesizing a compound and testing the compound in a binding assay, but that the specification fails to disclose a method having these steps.

While Applicants respectfully disagree with the Examiner’ s assertion such steps have no basis in the specification, in the interest of expediting prosecution of the instant Application, Claims 26, 34 and 41 have been canceled.

The Examiner has rejected Claims 28, 36 and 42 stating a disclosure in the specification of “80% amino acid homology” is not a fair basis for the limitation of “at least about 95%”. Furthermore, the Examiner states there is no contemplation in the specification of a method to produce a crystal with the cited sequence characteristics and having the stated spacegroup characteristics.

While Applicants respectfully disagree with the Examiner's assertion the specification fails to provide fair basis for the limitation "at least about 95%", in the interest of expediting prosecution of the instant application, Claims 28, 36 and 42 have been amend to specify the proteins used to produce the crystal have at least about 80% homology to the stated SEQ ID NO's. Support for sequences at least about 80% homologous to proteins represented by SEQ ID NO2, SEQ ID NO:4 and SEQ ID NO:6 can be found in the specification, for example, on page 136, lines 14-22, through page 137, lines 1-3. With regard to a limitation requiring the crystal belong to spacegroups P4₁2₁2 or R32, Applicants note this limitation has been removed from Claims 28, 36 and 42. However, Applicants have drafted new claims 45, 46 and 47, which depend from Claims 28, 36 and 42 respectively, which specify the crystal used in the methods of Claims 28, 36 and 42 belong to spacegroups P4₁2₁2 or R32. Applicants believe the specification supports the suggested combination of elements present in the combined claims. First, support for sequences having the cited characteristics has already been demonstrated above. Next, the specification, for example, page 19, lines 20-21, clearly teaches that crystals of the instant invention can belong to spacegroups P4₁2₁2 or R32. Finally, the specification states, for example, on page 18, lines 18-20, that crystals of the instant invention include crystals produced from proteins that are muteins or are represented by a 3D model of the present invention. Therefore, since the specification states proteins of the instant invention can have 80% homology to proteins represented by the specified SEQ ID NO's, and since the specification clearly states crystals of the instant invention, residing in specific spacegroups, can be made from proteins of the instant invention, Applicants contend the specification clearly supports the combination of elements, i.e. crystals in spacegroups P4₁2₁2 or R32 and made from proteins having 80% homology to proteins represented by the specified SEQ ID NO's. The fact that the two elements do not appear in the same location in the specification is irrelevant. The wording of the specification makes it clear proteins discussed in one part of the specification are intended to be used in making crystals described elsewhere in the specification. In view of this, Applicants request allowance of Claims 45-47.

The Examiner has rejected Claims 32-33 and 40 stating the specification does not disclose the concept of "structure-based design" nor what this concept is intended to embrace.

Applicants respectfully disagree. The specification, for example, page 143, lines 11-21, clearly state that methods to identify inhibitory compounds include designing compounds based on the 3D model of a FcR. This same section states that methods of using 3-dimensional models to design inhibitors are known to those skilled in the art. Furthermore, specific examples of computer programs which enable such design methods are listed in PCT Publication No. WO/95/35367, which was incorporated by reference; see, for example, page 143, lines 19-21. In addition to the support pointed to above, the Examiner's attention is directed to the specification, for example, page 146, lines 8-19, which clearly describe how a 3D model can be used to identify inhibitors. The cited section discloses that the method can include the step of identifying at least one amino acid in the IgE binding domain that interacts with the corresponding domain of Fc ϵ RI α . This section further discloses that the preferred inhibitory compounds will interact with one or more of those amino acids. While page 146, lines 8-22 do not disclose, specifically, with which amino acids an inhibitor should interact, such information can be found elsewhere in the specification; see, for example, page 151, lines 19-22, through page 171, lines 1-21. These sections of the specification describe in great detail regions of the IgE and Fc ϵ R α I proteins which interact and are crucial in formation of the complex. While these sections mostly relate to muteins and which amino acids should be altered to create such muteins, Applicants contend one skilled in the art would understand that the general information disclosed within these sections, (e.g., which amino acids directly interact) would apply to the above-referenced interaction described on page 146, lines 8-19. In view of this, Applicants request withdrawal of the rejection of Claims 32, 33 and 40.

The Examiner has rejected Claims 28-30, 36, 38 and 42 stating the specification does not disclose a three-dimensional model defined by coordinates obtained following crystallization. The Examiner further states the specification does not disclose producing models having a root mean square deviation of less than 10 angstroms from the coordinates Table 1. Applicants respectfully disagree. First, the specification, for example page 136, lines 1-11, clearly contemplates producing models having a root mean square deviation of less than 10 angstroms from the atomic coordinates in Table 1. Such a deviation allows for the natural variation expected in the measurement of atomic coordinates. That a small amount of variation in the

measurement of atomic coordinates is to be expected is acknowledge by the inventors by their use of the term “substantially”(for example, on page 135, lines 9-11) when describing models of the instant invention defined by the coordinate Tables. Next, the inventors clearly contemplated that such a model would be constructed by producing crystals and obtaining x-ray diffraction data from such crystals. In support of this statement, Applicants direct the Examiner’s attention to the specification, for example page 137, lines 11-20, which clearly state that one embodiment of the instant invention is a model produced by first producing a crystal and then obtaining x-ray diffraction data from the crystal. As note *supra*, Applications contend that even though disclosure of particular elements may not be contiguous within the specification, the wording of the specification makes it clear that the various elements of the instant invention are meant to be used in conjunction with one another. Therefore, in view of the above, Applicants assert the specification clearly supports producing models having a root mean square deviation of less than 10 angstroms from the atomic coordinates in Table 1, by a method in which crystals are produced and then x-ray diffraction data is obtained from those crystals.

Rejections Under 35. U.S.C. §112, second paragraph – indefiniteness

The Examiner has rejected Claims 23-44 under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Examiner states the terms “interact” and “interaction” are indefinite and the specification provides no clear definition of what is intended by these terms and there does not appear to be an art understood definition for these terms. Further, the Examiner state the wording in several of these claims is confusing and that several of these claims use terms lacking antecedent basis.

With regard to Claims 32, 37, 39, 40 and 43, Applicants direct the Examiner’s attention to the beginning of the Remarks section where Applicants have attended to the confusion and lack of antecedent basis in these claims.

With respect to the use of the terms “interact” and “interaction”, Applicants respectfully disagree with the Examiners assertion that such terms have no clear definition. At the very least, a general dictionary definition of “interact” is “to act upon each other.” Furthermore, the specification, for example page 144, lines 7-9, states an inhibitory compound should be capable

of physically and structurally associating with a FcR and/or antibody. Applicants contend that one skilled in the art would instantly understand that the specification, in discussing a compound “acting upon” a protein by “physically and structurally associating” with that protein, refers to the ability of the compound to bind to the protein. That such an association means “binding” is reinforced by the specification (for example page 144, lines 5-7) which states compounds can inhibit binding either competitively or non-competitively and can interact with the protein either at the binding site or allosterically. Applicants note that all of the terms used in the specification to describe the way in which a compound might inhibit the binding of IgE to Fc ϵ RI α are terms used in the art when referring to binding moieties, bolstering the idea that the inhibitor binds to IgE or Fc ϵ RI α protein. Therefore, in view of the above, Applicants contend the terms “interact” or “interaction” would not be indefinite to one skilled in the art.

Rejections Under 35 U.S.C. §103 – obviousness

The Examiner has rejected Claims 23-25, 27, 32-33, 35, 37, 39-40, and 43-44 under 35 U.S.C. §103 as being unpatentable over Freimuth (US 2003/0027338 A1). The Examiner states Freimuth discloses using atomic coordinates determined for a crystal structure of a complex between adenovirus bound to a cellular receptor. The Examiner furthers states this model is used to design or select inhibitors. According to the Examiner, the difference between the prior art and the claimed invention is the recited three-dimensional structure information which is fed into an algorithm for the purpose of comparing or modifying those data using steps that do not impose a change in the processing steps. The Examiner therefore concludes the three-dimensional data are nonfunctional descriptive material which, according to the Examiner, cannot render non-obvious an invention that would have otherwise been obvious.

To begin with, Applicants believe the Examiner was in error in failing to accord any patentable weight to the contents of the database of the instant claims. As stated under 35 U.S.C. §103, “A patent may not be obtained ...if the differences...are such that...the subject matter *as a whole* (emphasis added) would have been obvious at the time the invention was made..”. The key point here is that the invention must be examined as a whole. Applicants appreciate that the Examiner’s decision to not accord the contents of the database patentable weight was based on

her contention that such data constitutes non-functional, descriptive material. Applicants believe the key question here is whether the coordinate data can truly be considered non-functional.

Applicants do not agree with such a classification. The MPEP at 2106 IV B(1)(b) states that descriptive material is nonfunctional if it fails to create any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer, and therefore does not impart functionality either to the data as so structured or to the computer. The Examiner has stated the contents of the database are non-functional because the x-ray crystallographic data does not alter how the computer system functions, i.e., the database of the claimed computer system does not reconfigure the computer system to perform a different function than the computer system of Freimuth. Applicants disagree with this conclusion and contend the data representing the structural coordinates do create a functional interrelationship with the claimed computer system and that they do impart functionality to the computer system. The purpose of the claimed computer system is to produce a three-dimensional model of a complex between human IgE and a Fc ϵ RI α protein. Without specific coordinates, such a task would be impossible in that the computer would not have any guidance as to how to render the model. Therefore the function of the database contents is to provide guidance to the computer as to how to render the model of the IgE:Fc ϵ RI α complex. The computer processes and the database are interrelated in that by themselves, neither the coordinate data of the database nor the computer can produce the desired model. It is only through the interaction of the computer program and the coordinate data that such a model can be produced. Therefore, the contents of the database are essential for the computer processes and to the proper functioning of the claimed system. As stated by the court in *In re Bernhart and Fetter*,

"...if a machine is programmed in a certain new and unobvious way, it is physically different from the machine without that program; its memory elements are differently arranged. The fact that these physical changes are invisible to the eye should not tempt us to conclude that the machine has not been changed."

Extending this argument to the instant case, the fact that the effect of the structural coordinate

data on the computer processes is invisible to the eye should not lead one to think it has no effect or function. Clearly the coordinate data is instrumental in guiding the computer in its construction of a final model. Without such data, the processes responsible for producing the model would not be able to function and no model would be produced. As such, Applicants contend that the data is an integral part of the computer processes and therefore, such data must be included when considering the instant claims.

Finally, once it is accepted that the contents of the database should be considered as an element of the claim, Applicants believe there is then no basis for the obviousness rejection. It is well established that in order to establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art. (MPEP 2143.03) In the instant case, the prior art cited by the Examiner (Freimuth) does not describe a three-dimensional model of a complex between IgE and Fc ϵ RI α protein and it certainly does not disclose or suggest the instant coordinates. Without such teaching, Applicants assert that it would not have been obvious for one of skill in the art to arrive at the structures disclosed by the Applicants in the instant Application.

CONCLUSION

In view of the above Amendments and Arguments, Applicants request withdrawal of all rejections and solicit allowance of the submitted claims. In the event the Examiner has any questions regarding this Application, the Examiner is invited to contact the undersigned representative at (970) 493-7272.

Respectfully submitted,

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